MILITARY MEDICINE, 177, 5:484, 2012

Practice Guidelines for the Diagnosis and Management of Patients With Q Fever by the Armed Forces Infectious Diseases Society

MAJ Joshua D. Hartzell, MC USA; CDR Todd Gleeson, MC USN†; Stephanie Scoville, DrPH‡; Robert F. Massung, PhD§; COL Glenn Wortmann, MC USA*; CAPT Gregory J. Martin, MC USN**

ABSTRACT This issue in the series Current Topics in Military Tropical Medicine focuses on Q Fever. Q fever is a zoonotic infection caused by the bacterium *Coxiella burnetii*. Over 150 confirmed cases have occurred among U.S. military personnel deployed to Iraq since 2007. Acute Q fever is underdiagnosed because of a myriad of possible clinical presentations but typically presents as a flu-like illness. The most common chronic manifestation is endocarditis. Most providers are not familiar with the diagnosis, treatment, or appropriate follow-up of this disease. In order to facilitate the care of patients infected with *C. burnetii*, the Armed Forces Infectious Diseases Society convened a panel of experts in the field to develop practical guidelines for those caring for infected patients. The recommendations and rationale are reviewed in this article.

INTRODUCTION

The Armed Forces Infectious Diseases Society (AFIDS) convened a consensus panel of military infectious diseases physicians, public health professionals, and laboratory experts to address the evaluation and management of service members with Q fever. This "AFIDS Q Fever Working Group" was initially created in April 2008 by the Infectious Diseases Consultants from the Army, Navy, and Air Force. Additional participants included representatives from the U.S. Army Public Health Command (USAPHC), the Centers for Disease Control and Prevention (CDC), as well as Department of Defense (DoD) Infectious Diseases clinicians with experience in treating Q fever patients.

The following recommendations and rationale are for patients with clinical syndromes consistent with acute Q fever and for management and follow-up of patients with serologically confirmed Q fever. An algorithmic depiction of the advised approach is represented in Figure 1.

CLINICAL PRACTICE GUIDELINES FOR Q FEVER IN U.S. MILITARY

(1) The diagnosis of acute Q fever is typically made clinically and confirmed with serology. If polymerase chain reaction (PCR) is available, it provides an additional method for diagnosis.

*Infectious Diseases Service, Walter Reed National Military Medical Center, Building 7, 1st Floor, 8901 Rockville Pike, Bethesda, MD 20889.

†Department of Medicine, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814.

‡Epidemiology and Disease Surveillance, Army Institute of Public Health, U.S. Army Public Health Command, 5158 Blackhawk Road, Aberdeen Proving Ground, MD 21010-5403.

§Division of Vector-Borne Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, 1600 Clifton Road NE, MS G-13, Atlanta, GA 30333.

Series Editor: CDR David Brett-Major, MC USN

The series *Current Topics in Military Tropical Medicine* is an educational outreach program developed by the faculty of the U.S. Military Tropical Medicine program (MTM) and *Military Medicine*. MTM is a joint program which educates and trains military medical personnel in the practice of medicine in developing areas under the auspices of the Navy Medicine Professional Development Center. Questions and comments on this series should be directed to the series subeditor and Program Director, U.S. Military Tropical Medicine, Director.MTM@med.navy.mil.

Accreditation Statement: The Navy Medicine Professional Development Center (NMPDC), Continuing Medical Education (CME) Department, Bethesda, Maryland, is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for Physicians. NMPDC designates this Journal Activity for a maximum of 1.0 AMA PRA Category 1 Credit, per published event. Physicians should only claim credits commensurate with the extent of their participation in the activity. Credit must be claimed before December 31, 2012. AMSUS members may claim this credit through the survey and quiz at https://www.surveymonkey.com/s/Y29HZYS.

Disclosure Statement: All those involved in the planning and execution of this issue of Current Topics in Military Tropical Medicine (editors, authors, reviewers) report no disclosures.

The content herein represents the views of the authors and not NMPDC, Walter Reed National Military Medical Center, Army Public Health Command, Uniformed Services University, Centers for Disease Control, Departments of the Army, Navy, Defense, Health and Human Services, or any other agency of the U.S. Government.

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
MAY 2012		**00-00-2012 to 00-00-2012**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Practice Guidelines for the Diagnosis and Management of Patients With Q Fever by the Armed Forces Infectious Diseases Society	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) **Infectious Diseases Service, Walter Reed National Military Medical,Center, Building 7, 1st Floor, 8901 Rockville Pike,Bethesda,MD,20889**	8. PERFORMING ORGANIZATION REPORT NUMBER
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES
MILITARY MEDICINE, 177, 5:484, 2012

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT **unclassified**	b. ABSTRACT **unclassified**	c. THIS PAGE **unclassified**	**Same as Report (SAR)**	**12**	

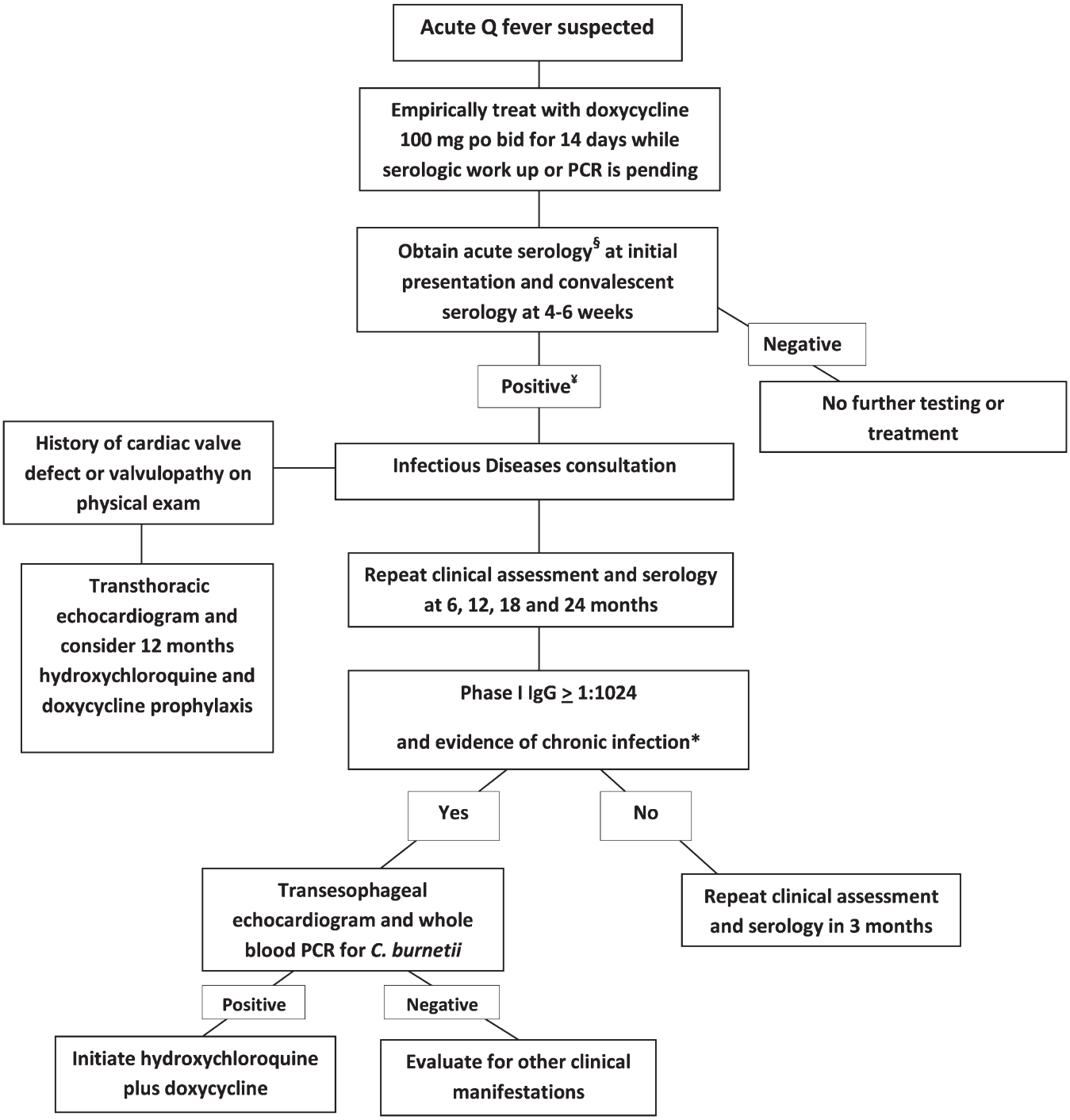

FIGURE 1. Algorithm for management of Q fever. §Serology should be performed at the same reference lab to minimize interlaboratory variability. ¥Report confirmed cases to public health/preventive medicine office. *Note: Clinical signs or symptoms consistent with possible chronic infection (fevers, chills, weight loss, shortness of breath, new heart murmur, elevated inflammatory markers) at anytime should prompt referral to Infectious Diseases.

(2) Acute Q fever cases should be treated with 14 days of oral doxycycline (100 mg) twice per day. In regions endemic for Q fever, empiric treatment with doxycycline is recommended for patients with a compatible clinical presentation as serology may be negative during the initial presentation and there may be a delay in receiving results from reference laboratories.

(3) Patients treated for Q fever should be referred for follow-up testing. When possible, acute serum samples should be obtained before initiation of empiric therapy and stored for later evaluation. In general, patients do not need medical evacuation from forward-deployed medical treatment facilities, and follow-up and testing should be performed upon redeployment.

(4) Doxycycline is not indicated for an asymptomatic individual who is retrospectively diagnosed with acute Q fever (typically as a result of diagnostic delays). Fatigue as the sole complaint does not warrant antibiotic treatment. Patients with a positive serology or PCR who were not initially treated and subsequently present with objective or subjective symptoms compatible with chronic Q fever should be referred to Infectious Diseases for evaluation.

(5) Serologic testing should be obtained at the time of clinical presentation and 4 to 6 weeks later (convalescent samples). Patients with negative convalescent samples should not be diagnosed with Q fever, and no further evaluation is indicated. Patients with positive samples should have repeat phase I and II IgM and IgG serologic testing every 6 months and be followed clinically for a period of 2 years or longer as the individual case may dictate (in consultation with Infectious Diseases). If the phase I IgG titer is still ≥1:1024 by the end of the second year, and equivalent to or greater than the phase II IgG titer, then further serological testing periodicity should be determined by an Infectious Diseases physician on a case-by-case basis, but should at least include testing at 36 months from acute infection.

(6) Patients with acute Q fever should have a complete blood count with differential, basic metabolic panel, liver-associated enzymes test, erythrocyte sedimentation rate, and C-reactive protein included in their initial laboratory evaluation.

(7) Screening transthoracic echocardiography (TTE) is not recommended for all patients diagnosed with acute Q fever. A TTE should be reserved for patients with acute Q fever and a known valvulopathy (e.g. bicuspid aortic valve), cardiac symptoms, or a significant cardiac murmur on physical exam.

(8) If a patient with acute Q fever is known to have a significant valvulopathy or is discovered to have one on exam, then 12 months of prophylactic therapy with hydroxychloroquine and doxycycline can be considered on a case-by-case basis in consultation with an Infectious Diseases specialist.

(9) Patients without cardiac valvulopathy or those with only minimal valvulopathy on echocardiography (trace/mild regurgitation) should not receive antibiotic prophylaxis though still can be treated for their acute Q fever as clinically indicated.

(10) Medical evacuation is not recommended for the purposes of obtaining a transthoracic echocardiogram unless there are clinical signs indicating a more urgent evaluation is indicated.

(11) If, during the follow up stage:

phase I IgG titers continue to rise above 1:1024
phase II IgG titers continue to rise but remain equal to or lower than phase I
there is clinical evidence of inflammatory disease

then the patient should undergo transesophageal echocardiography and whole blood PCR testing for *C. burnetii* (available at the CDC). In order to centralize testing, and to avoid the performance of any potentially unnecessary transesophageal echocardiography, these evaluations should be managed with or directly by an Infectious Diseases specialist.

(12) Any patient with a history of Q fever and a concern for chronic disease should be evaluated by an Infectious Diseases physician.

(13) All serum for Q fever testing in U.S. military service members should be sent to the U.S. Air Force School of Aerospace Medicine (USAFSAM) laboratory in Dayton, OH. USAFSAM will perform the Food and Drug Administration-approved IgM/IgG IFA. For patients not eligible for DoD services, a commercial laboratory that uses the Focus Diagnostics Q fever test or, preferably, a reference center such as a state laboratory or the CDC should be utilized. Follow-up serology should be performed at the same laboratory to minimize interlaboratory variability and misinterpretation of varying results.

BACKGROUND

Q fever is an infectious disease caused by the intracellular bacterium *C. burnetii*, which is typically associated with animals (particularly cattle, sheep, and goats).[1–3] The organism is excreted in feces, urine, and milk but is found in highest concentration in birth products. Humans primarily become infected through the inhalation of infectious aerosols. Direct animal contact is not required for infection as the spore-like form of *C. burnetii* can persist in the environment for months and can be airborne.[1] Transmissions through sexual contact or from the bite of infected ticks have been reported but are rare and not considered to be significant modes of human infection.[1,4–6] *C. burnetii* is exceptionally infectious making it a potential agent of biowarfare; however, these guidelines will only address the management of naturally acquired Q fever.

The incubation period for acute Q fever is typically 2 to 3 weeks but may vary depending on the size of the inoculum.[1] An estimated 60% of acute infections are asymptomatic. Symptomatic acute Q fever usually presents as one or a combination of the following three syndromes: an acute self-limited febrile syndrome (flu-like illness) of several days to weeks with no localizing findings, pneumonia, and/or hepatitis. Moderate to severe headache is a frequent finding in acute disease. Other clinical manifestations include meningitis, orchitis, and cholecystitis, and virtually all organ systems have been reported to be affected.[1–3,7]

Chronic *Coxiella* infection follows a very small percentage of acute cases and usually occurs in patients with some level of immunocompromise or cardiac valvulopathy.[1] The median time to development of chronic Q fever was 3 months

in one French case series,[8] but can occur from a month to years after initial infection.[1,7] Manifestations of chronic infection may include endocarditis, other endovascular infections, granulomatous hepatitis, and osteomyelitis.[2,7]

U.S. MILITARY Q FEVER CASES

In addition to published cases,[9–18] over 150 cases have been confirmed by the USAPHC among U.S. military personnel serving in Iraq since 2007. An evaluation of pre- and post-deployment sera from U.S. military personnel deployed to Iraq and hospitalized from April 2003 to December 2004 suggested that Q fever is a significant infectious disease threat in Iraq. Overall, 10% with diagnostic codes consistent with acute Q fever symptoms had evidence of *Coxiella* seroconversion.[17] A range of clinical manifestations from pneumonia, hepatitis, and febrile syndromes to less common presentations of cholecystitis and meningoencephalitis have occurred.[9–17] In May 2010, the CDC identified Iraq as an important regional exposure site for *C. burnetii* because of the increased number of Q fever cases among U.S. military personnel.[19]

DIAGNOSIS OF Q FEVER

Many physicians may be unfamiliar with Q fever, leading to delayed diagnosis in both acute and chronic infections. The diagnosis of Q fever, at any stage, can be difficult given the potential reliance on imprecise, poorly standardized assays.[20] Diagnostic tests for acute disease are discussed here, whereas the approach to the diagnosis of chronic disease and appropriate follow-up is complex and is discussed separately.

Culture

The culture of *Coxiella* from blood or tissue is highly specific for the diagnosis of Q fever, but is insensitive and poses a significant infection risk to laboratory personnel without proper biosecurity measures. Culture requires specialized cell or yolk sac media which are not readily available nor commonly used in routine microbiological evaluations. Consequently, the use of culture for the diagnosis of Q fever is rarely done outside specialized centers.

Serology

A basic understanding of the antigenic phases of *C. burnetii* is critical to interpreting the results of serologic testing. *C. burnetii* exists in two antigenic forms that are determined by changes in the surface lipopolysaccharide: phase I and phase II. The virulent phase I is found in vivo in animals and humans, whereas the avirulent phase II develops in vitro only after repeated passage of the organism in cell or egg culture.[3] Clinicians may be confused that phase II antibodies appear before phase I antibodies during the course of an infection. Phase II antibodies develop at approximately 2 weeks, and 90% of patient serum specimens are positive within 3 weeks.[20] A four-fold rise in phase II IgG antibody titer between acute and convalescent samples is used to confirm the diagnosis of Q fever. Phase I antibodies appear later and recurrence or persistence of high levels of phase I antibodies, in combination with constant or falling levels of phase II antibodies and other signs of inflammatory disease, should raise suspicion of possible chronic Q fever.[20] Phase I and II antibodies may persist for months or years after initial infection.[10,16,21,22]

Several different *Coxiella* serologic methods exist for laboratory diagnosis, including indirect immunofluorescence assay (IFA), complement fixation test, and enzyme linked immunosorbent assay. Most authorities consider the IFA the gold standard.[1] Although paired sera demonstrating seroconversion is preferred, a single sample with a phase II immunoglobulin G (IgG) titer of ≥1:200 and immunoglobulin M (IgM) ≥1:50 is diagnostic criteria for acute Q fever using the French National Reference Center (NRC) IFA.[1] The CDC utilizes its own (non Food and Drug Administration [FDA]-approved) Q fever IFA. With this IFA, a phase II IgG titer of ≥1:128 is considered positive for surveillance and a four-fold rise in titer between acute and convalescent sera confirms acute Q fever.[17,19] The U.S. Air Force School of Aerospace Medicine (USAFSAM) is the only DoD laboratory approved to perform Q fever serologic testing. Since the initial consensus meeting of the AFIDS Q fever Working Group in 2008, Military Treatment Facilities were requested to send patient specimens for Q fever serology to USAFSAM to minimize interlaboratory variation; however, some Military Treatment Facilities still send specimens to commercial laboratories (e.g. Quest and Labcorp). USAFSAM and these two major commercial laboratories use the same FDA-approved Q fever IFA manufactured by Focus Diagnostics (Cypress, California). Specific cutoffs for IgG and IgM titer levels vary between laboratories and reference ranges for the particular testing method should be used when interpreting the results.

Interpretation of Serologic Results

Unfortunately, using serologic assays to diagnosis Q fever can be problematic, and several recent studies have highlighted inconsistencies with the available assays. Parallel testing of samples by the Focus Diagnostics IFA and the French NRC IFA revealed marked differences in titer values from several U.S. military patients with Q fever.[16] A recent study examined the concordance of serological and polymerase chain reaction (PCR) results for a well defined cohort of Q fever patients by 3 separate international reference laboratories.[23] Patients followed for 6 years from an outbreak had samples tested at laboratories from the United Kingdom, France (NRC), and Australia. The laboratories used the same microimmunofluorescence testing method with different antigens and growth substrates. Surprisingly, only a 35% concordance among the laboratories was reported. Ten patients had a chronic serological profile based on U.K. results, but there were no chronic serological profiles from the other two laboratories. The authors questioned whether an "indiscriminate" cutoff of 1:800 should be used and cautioned the use of these

cutoffs alone to make clinical decisions.[23] These studies raise important questions regarding the validity and reliability of serological testing for Q fever, and remind the clinician to incorporate the patient's clinical presentation when securing a diagnosis and formulating a treatment plan.

Nucleic Acid Based Testing

Given the potential weaknesses of serological testing, alternative diagnostic assays have been developed. Real-time polymerase chain reaction (RT-PCR) testing has been used for diagnosis in both acute and chronic disease. RT-PCR may detect *C. burnetii* DNA before serology is positive and typically becomes negative as the serologic response develops.[24] In an evaluation of RT-PCR during the recent and ongoing Dutch outbreak of Q fever, the following serum samples were positive by PCR: 49 of 50 (98%) acute serum samples from seronegative patients, 9 of 10 (90%) serum samples from patients with only phase II IgM, 3 of 13 (23%) serum samples with phase II IgM and IgG, 2 of 41 (5%) serum samples with phase II IgM and IgG and phase I IgM, and 0 of 15 (0%) serum samples with both IgM and IgG antibodies reactive with both phase I and II antigens.[25] The latest time point after onset of disease at which *C. burnetii* DNA could be detected was on day 17.

Hamilton et al[18] reported the effectiveness of the Joint Biological Agent Identification and Diagnostic System (JBAIDS) (Idaho Technology, Salt Lake City, Utah) Q Fever Detection Kit to diagnose acute Q fever. The JBAIDS system is a portable PCR system designed for use in a forward-deployed laboratory. Results of testing for Q fever can be available within 4 hours. Their study examined patients presenting to a combat support hospital in Iraq with undifferentiated fever. Six of nine patients who had Q fever confirmed by serology had a positive PCR, and there were no positive PCR results among 9 patients that tested seronegative for Q fever.

The combination of these reports suggests that PCR is useful in confirming the diagnosis of acute disease. In May 2011, the FDA approved the JBAIDS Q Fever Detection Kit for the diagnosis of Q fever in designated DoD laboratories. Although this is promising, it is unlikely that the assay will be widely available for clinical use. JBAIDS-equipped labs in forward-deployed hospitals could help differentiate febrile illness in areas endemic for Q fever.

Detection of *Coxiella* DNA may be helpful in diagnosing chronic Q fever and has been recommended in the evaluation of suspected chronic Q fever infection.[8] Whole blood *Coxiella* PCR may be positive in 64% to 100% of Q fever endovascular infections, with a reported specificity as high as 100%.[26] In a long-term study of endocarditis conducted in France, PCR on blood or serum samples was positive in 23 of 70 patients (33%) tested.[27] In a follow-up of 686 patients from the Dutch outbreak, 11 patients were diagnosed clinically with chronic infection, and PCR results were positive for 8 of these patients.[28] However, 4 of the 8 had repeat tests which were negative. Additionally, 9 patients without suspicion for chronic Q fever tested positive, including 2 in duplicate testing. None of the negative controls were positive, and the authors concluded that the results may have represented true infection or possible contamination. PCR results should be interpreted in the context of the patient and performed at a clinical reference laboratory.

PCR can also be used to detect *Coxiella* in excised valvular tissue. A positive PCR result most often represents ongoing infection, but can rarely be associated with nonviable organisms following treatment.[27] PCR should be performed whenever possible on excised heart valves if Q fever is considered in the differential diagnosis.

RISK OF CHRONIC Q FEVER AND APPROPRIATE FOLLOW-UP

The risk of developing chronic Q fever in patients with acute Q fever has historically been believed to be near 1%, but is reportedly increased in patients with known risk factors to include pregnancy, immunosuppression, or known valvulopathy. Endocarditis is the most serious complication of chronic Q fever, and in those with pre-existing cardiac valvulopathy (mitral and/or aortic insufficiency and mitral or aortic prosthesis) may be as high as 39%.[29] This estimate is based on a small number of patients at one center and has been contested in the literature as recent studies have found no endocarditis in similar patients.[21,30]

Given the uncertainty of the risk of developing chronic Q fever, the appropriate follow-up for patients with acute Q fever remains complicated and controversial. Current recommendations for the follow-up of patients with acute Q fever and the diagnosis of chronic Q fever (endocarditis) rely on serologic cutoff values that are specifically based on the French NRC IFA. These values were based on studies involving older patients with comorbid illness, and generalizing this data to a younger, U.S. active duty military population is problematic. The French NRC has historically considered a single phase I IgG titer of ≥1:800 by microimmunofluorescence as diagnostic of chronic infection and this cutoff has been included as one of the major Duke criteria for the diagnosis of endocarditis.[8,29,31,32] The phase I IgG titer is usually higher than the phase II IgG in chronic infection; however, these titers may be equivalent.[33] Confusingly, there have been discrepancies as to whether the cutoff is >1:800 or ≥ 1:800.[1,7,8,31–35] Recent studies, including one from the French NRC, have led to revisions of the original recommended follow-up strategy.[36]

Endocarditis

In 2001, Fenollar et al[29] published a retrospective review of 1,569 patients diagnosed with acute Q fever between 1985 and 2000. Twelve of these patients developed endocarditis (0.76%), and the mean age was 60 years (range 45–74) and all had known pre-existing valvular disease. Endocarditis was

diagnosed by modified Duke criteria 1 to 18 months after acute Q fever (mean 6 months) although echocardiography revealed cardiac vegetations in only 3 of 12 patients.

To further identify risk factors for the development of endocarditis, these investigators compared 102 patients with Q fever endocarditis to 200 randomly selected acute Q fever patients who did not develop endocarditis.[29] Ninety-five of the 102 endocarditis cases (93%) reported previous valvulopathy. Of the 7 patients without pre-existing valvulopathy, 3 patients had an active lymphoma and 2 had an active solid organ cancer at the time of Q fever endocarditis. In the comparison group, only 6 of the 200 control patients without endocarditis had previously known valvular disease. Those without endocarditis had a significantly lower prevalence of cancer ($p = 0.004$) and pre-existing valvulopathy ($p < 0.001$).[29]

This report also evaluated 31 patients with pre-existing valvulopathies who had acute Q fever and identified 12 (38.7%) who developed endocarditis.[29] The type of pre-existing valvular disease did not influence a progression to endocarditis. Among 8 patients who received no antibiotics, 6 (75%) developed endocarditis. For 10 patients who received doxycycline alone (duration 2 weeks to 6 months), 5 developed endocarditis. Of the 12 patients who received both doxycycline and hydroxychloroquine (HCQ; duration 1 month to 15 months), none developed endocarditis. Based on these data, the authors recommended that any patient with acute Q fever and known pre-existing valvulopathy receive prolonged doxycycline/HCQ combination therapy in order to prevent Q fever endocarditis.[29] A duration of 12 months of prophylactic therapy was suggested based on the longer duration (1 to 15 months) of therapy received by the patients who did not develop endocarditis.

In 2006, Fenollar et al[37] reported a case series of 3 patients without known pre-existing valvulopathy but who developed chronic Q fever. The first patient was a 45-year-old male treated with 21 days of doxycycline who presented 5.5 years later with aortic valve endocarditis requiring valve replacement. The second patient was a 53-year-old woman with acute Q fever who received 21 days of doxycycline and presented 2 months later with fever, mitral valve prolapse, mitral valve vegetations, and a positive serum *Coxiella* PCR. The third case was a 50-year-old male treated with 21 days of doxycycline, with a normal transthoracic echocardiography (TTE) at that time. Seven months later, a workup for fever showed trivial mitral valve insufficiency, a mitral valve vegetation, and an elevated Q fever phase I IgG titer (1:1600). Based on these 3 cases, the authors advocated a screening TTE for patients with acute Q fever in order to detect pre-existing valvulopathies that might be risk factors for endocarditis.

In 2007, Landais et al[8] reported the serological evolution from acute Q fever to endocarditis in 22 patients (14 men and 8 women) with a median lag time of 3 months. The mean age was 60 years (range, 44–76 years). Seventeen (77.2%) had known cardiovascular abnormalities, and 5 patients had no known valvulopathy (3 of these patients were previously reported).[37] Of 17 patients with pre-existing valvulopathy, 12 (70.5%) had pre-existing valvular insufficiency, 2 (11.7%) had prosthetic valves, 1 (5.8%) had mitral valve prolapse, and 2 (11.7%) had valvular stenosis. The diagnosis of endocarditis (by modified Duke criteria) in this case series was definite in 5 patients (22.7%) and only possible in 17 patients (77.2%). Based on this data, the investigators strengthened the previous recommendation for performing a screening TTE on all patients with acute Q fever. They further recommended 12 months of prophylactic therapy with doxycycline and HCQ for patients with acute Q fever and any level of valvulopathy (including "trivial" or "mild" valve regurgitation and mitral valve prolapse) to prevent infective endocarditis.[8,29,37] The authors recommended all patients have serologic follow-up at 3 and 6 months, and a TEE as well as *C. burnetii* PCR from a blood sample if a phase I IgG rises above ≥1:800. The authors suggested that, if either test is abnormal, the patient receives treatment for at least 18 months with doxycycline and HCQ. For patients with a phase I IgG titer which remains <1:800 at 6 months, no further serologic follow-up is required.[8] These recommendations were largely untested in other populations, but given lack of available evidence were incorporated into the initial, unpublished AFIDS Q fever guidelines disseminated to military physicians. Additionally, these recommendations were published in other venues as the standard approach to patients diagnosed with Q fever.[38]

A recently published study on 510 collegiate athletes undergoing sports screening showed that all major valve abnormalities (bicuspid aortic valve, pulmonic stenosis, and mitral valve prolapse) were identified on physical exam.[39] This data suggest that TTE is not required to screen for these cardiac abnormalities as a skilled physician can detect valvulopathies which might predispose patients to chronic Q fever.

As mild mitral regurgitation may be seen in as many as 10% of healthy, young adults,[40] the recommendation to administer 12 months of doxycycline and high dose HCQ to all patients with acute Q fever and mild mitral regurgitation would likely produce more iatrogenic harm than benefit. The absolute risk of developing chronic Q fever in patients with "trivial," "trace," or "mild" valvular regurgitation detected on echocardiography is not known, but the risk is believed to be low.[21,30,41,42] Data from the Netherlands, Taiwan, France and the U.S. military cohort discussed below do not support screening echocardiography on all patients with acute Q fever. Instead, we suggest a more pragmatic approach of performing TTE only on patients with significant murmurs detected on physical exam or on patients with a history of valvulopathy.

Serological and Clinical Follow-up

In 2010, two different groups of investigators published data using the commercially available Focus Diagnostics

Q fever IFA instead of the IFA used by the French NRC. Analyzing the recent outbreak in Taiwan, investigators prospectively utilized the Focus IFA, but applied the French NRC IFA phase I IgG titer cutoff of ≥1:800 for a diagnosis of chronic infection. A total of 120 consented subjects who had experienced acute Q fever were studied.[21] In the first cohort of 92 persons (infected in 2004–2007), 17 (18%) had serologic profiles suggestive of chronic Q fever (titers of phase I IgG of 1:1280 to 1:5120) after a median follow-up period of 606.5 days. After a further follow-up period (median 592 days) exclusively for those 17 subjects, serological resolution with four-fold decrease of titers of phase I IgG was noted in only 5 (29%). In the second cohort of 28 patients acutely infected in 2009, only 1 (4%) had high levels of phase I IgG 180 days after acute Q fever. All 18 subjects from both time periods with high phase I IgG titers in this report were asymptomatic and had negative serum PCR testing. None of the 120 patients followed developed chronic Q fever. These investigators chose continued serological and clinical monitoring as the rational strategy for patients with high levels of phase I IgG who were "asymptomatic or with vague discomforts."[21] They concluded that a phase I IgG titer ≥1:800 alone should not be used to diagnose chronic infection. A recommendation for duration of follow-up was not provided by this study as only 5 of the 18 patients demonstrated serological resolution (four-fold decrease in the phase I IgG titer) during the 592 days of follow-up.[21]

A study from the Netherlands that followed 686 patients with acute Q fever not only supported the use of clinical symptoms to guide treatment decisions but called into question the Phase I IgG titer cutoff of 1:800.[28] Eleven cases of chronic disease, defined as meeting two of three of the following criteria: Phase I IgG titer ≥ 1:1024, a positive PCR at least 3 months after the acute infection, or clinical or radiological signs supporting chronic Q fever were identified. Six of these patients had known risk factors for chronic disease. Thirty-five patients (5%) had serological evidence of chronic disease (IgG phase I titer ≥1:1024) but without clinical signs of disease. A Phase I IgG titer of 1:1024 at 6 months had the best sensitivity (89%) and positive predictive value (16%) for confirmed chronic disease. High titers (phase I titer ≥1:1024) at 3 months were not predictive of chronic disease (positive predictive value 4%). Given the overall poor positive predictive values of the serological cutoffs for the detection of chronic Q fever, the authors recommended that the decision to diagnose and treat chronic Q fever should be "based primarily on clinical grounds." Based on a detailed description of titers over time, they recommended serological follow-up of acute Q fever cases at 3 and 9 months for patients with and without risk factors, respectively.

Especially noteworthy is an article published from the French NRC in 2011 that suggested that the 1:800 antibody titer should no longer be used because its positive predictive value was only 37%.[36] The authors reviewed 3,723 cases referred to the French NRC from 1985 to 2009. They reported on the positive predictive values at different cutoffs and concluded that the phase I IgG titer cutoff should be increased to ≥1:1,600. However, the positive predictive value at this cutoff was only 59%.

Another report from France cautioned the use of serological values alone in determining the presence of chronic infection. They retrospectively reported on 35 patients diagnosed with chronic Q fever and noted that 23 (66%) of the patients were asymptomatic. Nine of these patients had not been treated yet were healthy. The authors concluded that PCR of the blood for *C. burnetii* and clinical symptoms should guide decision making rather than serology results.[43]

Following the Q fever outbreak in the Netherlands in 2007, Limonard et al[30] performed complete history and physical examinations at 6 and 12 months after the initial day of illness following a single baseline screening TTE. Serial serologic testing utilizing the Focus Diagnostics IFA was performed at baseline and at 3, 6, and 12 months. The mean age of this Q fever cohort of 85 patients was 49 years (range 18-80), and persistent symptoms after acute Q fever were reported by 59% and 30% at 6 and 12 months follow-up, respectively. These investigators observed an increase in both phase I and phase II IgG titers at 3 months with a subsequent decrease over the next 9 months. Screening echocardiography was done for 66 (78%) of the 85 Q fever patients. Structural cardiac abnormalities and valvular defects were classified according to the American Society of Echocardiography guidelines,[44–47] which define major (or clinically significant) valvulopathies as moderate and severe regurgitation or stenosis of the mitral and/or aortic valve. Minor valvulopathies are defined as trace or mild regurgitation or stenosis of the mitral and/or aortic valve, a bicuspid aortic valve and mitral valve prolapse without significant accompanying stenosis or regurgitation. Based on these definitions, cardiac valvulopathy was present in 39 (59%) patients, 5 of whom had a major or clinically significant (moderate or severe) valvulopathy. None of the 85 patients developed chronic Q fever.[30] Phase I IgG titers equal to or greater than 1:800 were found in 7/85 (8%) at time of diagnosis, in 21/85 (25%) at 3 months, in 13/85 (15%) at 6 months, and in only 2/85 (2%) at 12 months. The investigators noted that "although at the various time-points of follow-up there were patients with a phase I IgG titer of 1:1,024 or higher, suggesting chronic Q fever, none of these patients developed a clinical picture compatible with chronic Q fever."[30] These investigators noted that the cutoff value of ≥1:800 is based on a single-center experience using a laboratory developed IFA test and that studies are needed to compare commercially available assays with the French NRC IFA. This report noted that the absolute risk of developing chronic Q fever in patients with minor valvulopathies is unknown and that the limited number of patients in their study did not allow the determination of this risk. However, it is likely that the absolute risk is small enough to preclude the necessity of a screening TTE and

to defer prolonged prophylactic antibiotic treatment unless closely monitored serologic and clinical follow-up suggests chronic infection.[30] Based on this study, screening echocardiography is no longer performed as part of the standard evaluation of Q fever patients in the Netherlands.[30] Instead, close clinical and serological monitoring is performed for a period of 1 year (at 3, 6, and 12 months) and only when serological and/or clinical signs of chronic disease appear is further investigation using PCR and echocardiography undertaken. Furthermore, in patients with known, pre-existing risk factors for chronic disease, including cardiac valvulopathy, decisions regarding follow-up and prophylactic antibiotic treatment are made in each individual case by a multidisciplinary team including a medical microbiologist, an infectious diseases physician, and a cardiologist.[30]

A preliminary, unpublished analysis of USAPHC surveillance data regarding U.S. military Q fever cases has found similar serologic and echocardiograph findings as the Dutch cases. Among these cases, IgG titers have slowly declined over 2 years and at least 60% appear to have trivial left-sided valvulopathies identified during baseline echocardiographic screening. (Stephanie Scoville, DrPH, Mark Johnson, MD, personal communication) The serial serologic trend of the phase I and phase II IgG levels, combined with a clinical evaluation of the convalescent patient, has proved most useful in follow-up of acute Q fever patients.[28] Interpretation of serology from different laboratories has revealed significant inter- and intralaboratory variability that has led to further difficulty in making definitive serologic diagnoses.[16] To our knowledge, no incident cases of endocarditis have occurred.

Currently, the ideal follow-up of patients with acute Q fever remains undefined. The previous recommendations to perform serology every 3 months and to perform TEE and *Coxiella* PCR on those with Phase I antibody titers ≥1:800 are based on data which has not been validated, as discussed previously. Therefore, we recommend clinical and serologic follow-up for patients with acute Q fever, but that only patients exhibiting clinical signs or symptoms of chronic disease undergo further evaluation with TEE and PCR (Fig. 1). Given the complexity of these issues, we suggest that patients with possible chronic Q fever be referred to an infectious diseases specialist familiar with the disease.

TREATMENT

The treatment of Q fever depends on the stage of disease (acute versus chronic). The majority of the data comes from cohort studies, not randomized controlled trials, limiting the ability to effectively determine the optimal treatments. The recommendations below are based on expert opinion of the available studies (Table I). Multiple antibiotics have activity against *C. burnetii*, including tetracycline derivatives, trimethoprim-sulfamethoxazole (TMP-SMX), fluoroquinolones, and rifampin, but susceptibility testing is not routinely available.[1,48–51] Resistance to doxycycline appears to be rare.[51] Recent evidence demonstrated that tigecycline had improved *in vitro* activity compared to doxycycline, although it was not bactericidal and no clinical experience has been reported.[52]

TABLE I. Treatment Recommendations for Q Fever

Acute, Symptomatic Disease
Primary
Doxycycline 100 mg orally twice a day for 14 days
Alternate
Moxifloxacin 400 mg daily for 14 days
[a]Pregnancy: Trimethoprim/sulfamethoxazole (160/800 mg) DS twice a day until delivery
[a]Chronic Disease (Endocarditis, Vascular Infection, Osteomyelitis)
Doxycycline 100 mg twice a day plus HCQ 200 mg three times a day for 18 months minimum
Duration based on clinical response and underlying condition/ valvular defect
Pregnancy: Trimethoprim/sulfamethoxazole DS twice a day until delivery (duration of pregnancy then consider change to doxycycline and HCQ)

[a] Pregnant patients and those with chronic disease should be managed only in conjunction with infectious diseases specialist familiar with Q fever.

Treatment of Acute Disease

The treatment of choice for acute Q fever is oral doxycycline 100 mg taken twice a day for 14 days.[1,53–55] The only randomized controlled trial for the treatment of Q fever pneumonia compared erythromycin and doxycycline.[53] Patients treated with doxycycline resolved their fever 1.5 days faster than those treated with erythromycin and reported fewer gastrointestinal side effects.

A subsequent report of 63 cases supported these findings, demonstrating faster fever resolution with doxycycline than erythromycin (26 hours versus 98 hours, $p = 0.001$).[56] Another study from Greece reported outcomes for 113 patients with acute Q fever. Patients who received doxycycline (2.4 days, $p < 0.05$) defervesced faster compared to clarithromycin (3.3 days).[54] Clarithromycin was superior ($p < 0.001$) to beta-lactams (6.4 days). A retrospective study of 77 patients from Croatia showed similar efficacy between moxifloxacin, clarithromycin, and doxycycline.[57] The time to resolution was not significantly different but favored clarithromycin (1.9 days) and moxifloxacin (2.2 days) compared to doxycycline (2.4 days).

A recent large retrospective study from the Netherlands reported treatment outcomes in 438 patients and confirmed these earlier studies by demonstrating that doxycycline was the most effective antimicrobial measured in terms of reducing hospitalization (odds ratio 0.04, 95% confidence interval: 0.01–0.22).[55] Moxifloxacin outperformed azithromycin in this study and may be the preferred second line agent. Azithromycin was not considered effective therapy and was used as part of the reference group of antibiotics based on previous in vitro studies.[49]

Treatment appears to be most effective when given early in the disease course, but some patients respond even after having been febrile for a week or longer.[38,55] Treatment is not beneficial and should not be given after the symptoms of acute infection have resolved. Fluoroquinolones and macrolides (clarithromycin > azithromycin) are alternatives for patients unable to tolerate doxycycline.[1,55–58]

Treatment During Pregnancy

Pregnant women or children with acute, symptomatic Q fever should be treated with TMP-SMX because of the potential adverse effects of doxycycline and fluoroquinolones. The largest study to date examined TMP-SMX in 53 pregnant patients.[59] Sixteen patients who received TMP-SMX for at least 5 weeks during pregnancy were compared to 37 patients who did not. Women treated with TMP-SMX had decreased maternal chronic Q fever ($p = 0.001$), placental infection ($p = 0.038$), and obstetric complications ($p = 0.009$).[59] The authors recommended that pregnant women be maintained on TMP-SMX (320/1600 mg) until delivery and that treatment for more than 35 days obviated the need for treatment postdelivery. The risk of neonatal hyperbilirubinemia needs to be considered when using TMP-SMX, and thus treatment should be discussed with a Q fever expert. Importantly, a recent study from the Netherlands reported on 1174 pregnant women recorded in the Netherlands Perinatal Registry and there was no increased risk of adverse outcomes in those with a positive Q fever serology.[60] An ongoing study in the Netherlands is hoping to provide a more definitive answer to the risk of Q fever during pregnancy.[61]

Treatment of Chronic Disease

Treatment of Endocarditis

A full review of the treatment of Q fever endocarditis is beyond the scope of this guideline. Given the complexity and lack of evidenced based trials, Q fever endocarditis is best managed in conjunction with a specialist. An overview of the treatment is provided below (Table I), but it should be emphasized that the treatment of these patients must be individualized based on disease severity, underlying immune and valvular status, and response to treatment. Depending on the severity of the infection, surgical excision and valve replacement should be considered. The determination for surgery should be based on the patient's clinical condition and hemodynamic status, and not Q fever titers. Surgery is not always necessary to cure the infection.[27] Clinical responsiveness is often based on improvement in clinical symptoms and a serological resolution. A four-fold decrease in the phase I IgG and IgA titers and the disappearance of phase II IgM at 1 year have been suggested as evidence of cure.[27]

Multiple regimens of antibiotics have been used in attempts to treat Q fever endocarditis[42]; however, doxycycline plus HCQ have become the standard of care given their ability to confer bactericidal activity.[62] A trial comparing doxycycline plus a fluoroquinolone ($n = 14$) versus doxycycline plus HCQ ($n = 21$) demonstrated that the latter treatment was associated with shorter treatment durations (24 months) and fewer relapses.[63] There were no differences in mortality, need for valve surgery, or tolerance to the regimens. A larger follow-on study reported that the failure to add HCQ was associated with decreased serological responsiveness to treatment.[27] The same study demonstrated that failure to treat for 18 months resulted in more relapses. The current treatment recommendation for native valve and prosthetic valve Q fever endocarditis is to administer therapy for 18 or 24 months, respectively.[27] Obtaining doxycycline serum levels to monitor treatment may be useful, but clinical experience is limited and it is not routinely recommended.[64,65]

Some experts recommend serological follow-up for patients with Q fever endocarditis, although the exact length of monitoring is unknown. Million et al recommended periodic serological testing over 5 years, although some have advocated life-long monitoring.[27,66] A recent study from Spain showed the resolution of phase I IgG titers to <1:400 did not predict treatment outcomes.[67] Based on the available data and lack of other objective measurements, we suggest that patients with proven Q fever endocarditis have periodic serological testing for 5 years. Patients without an appropriate fall in titers should be followed longer on an individualized basis.

Treatment for Osteomyelitis and Vascular Infections

The treatment of other forms of chronic Q fever (including vascular infections and osteomyelitis) is not well studied and is based mainly on case reports or case series. Management decisions are best made on an individual basis, and these cases should be discussed with an expert on Q fever. Treatment for osteoarticular infections often involves surgical debridement and prolonged therapy (18 months) with doxycycline and HCQ.[68] Vascular graft or aortic aneurysm infections are extremely rare.[69] Patients receiving surgical treatment in conjunction with prolonged HCQ and doxycycline may have better outcomes.[69]

RISK OF HCQ THERAPY

The risks of therapy must be weighed when considering using HCQ as part of a prophylactic approach to prevention and treatment of Q fever.[8] Irreversible retinal toxicity from HCQ is rare; however, the risk dramatically increases after 5 years of use or a cumulative dose of 1000 g.[70] Treatment durations for Q fever are comparatively much shorter than the durations used for rheumatologic diseases, although it should be noted that the recommended dose for Q fever (600 mg per day) is above the usual dose of 400 mg daily prescribed for connective tissue diseases. Given the potential toxicity, the American Academy of Ophthalmology recommends a baseline eye exam followed by annual screening exams after 5 years. For those at high risk, annual exams should begin sooner. Patients at higher risk include those taking a daily dosage >6.5 mg/kg/day of HCQ, increased length of usage,

or medical status. Visual field (10-2 automated) testing should be combined with at least one of a group of newer, more sensitive tests, to include multifocal electroretinogram, spectral domain optical coherence tomography, and fundus autofluorescence. Based on the available data and inexperience with the higher dose of HCQ used in Q fever patients, the following screening is recommended: retinal exams should be done at baseline and repeated yearly while patients are taking 600 mg of HCQ per day.

SUMMARY

The body of literature regarding Q fever, particularly the laboratory diagnosis and appropriate follow-up and prevention strategies, has evolved significantly over the past 5 years in part because of the data generated from the recent Dutch outbreak. The approach advocated in these guidelines consolidates this literature and provides a practical approach for providers within the military health system.

ACKNOWLEDGMENTS

The authors would like to thank members of the Armed Forces Infectious Disease Society for sharing their expertise in managing patients with Q fever. The authors thank David Byers, Nicholas Conger, Patrick Danaher, Duane Hospenthal, Kent Kester, Clinton Murray, and Roseanne Ressner for their thorough review of this article. The MTM Course faculty express their sincere appreciation to the senior advisor for this educational project, CAPT Philip Coyne, MD, USPHS, for his guidance, expertise, and professional insight.

REFERENCES

1. Maurin M, Raoult D: Q fever. Clin Microbiol Rev 1999; 12: 518–53.
2. Parker N, Barralet JH, Bell AM: Q fever. Lancet 2006; 367: 679–88.
3. Raoult D, Marrie T, Mege J: Natural history and pathophysiology of Q fever. Lancet Infect Dis 2005; 5: 219–26.
4. Miceli MH, Veryser AK, Anderson AD, Hofinger D, Lee SA, Tancik C: A case of person-to-person transmission of Q fever from an active duty serviceman to his spouse. Vector Borne Zoonotic Dis 2010; 10: 539–41.
5. Milazzo A, Hall R, Storm PA, Harris RJ, Winslow W, Marmion BP: Sexually transmitted Q fever. Clin Infect Dis 2001; 33: 399–402.
6. Kruszewska D, Lembowicz K, Tylewska-Wierzbanowska S: Possible sexual transmission of Q fever among humans. Clin Infect Dis 1996; 22: 1087–8.
7. Raoult D, Tissot-Dupont H, Foucault C, et al: Q fever 1985-1998. Clinical and epidemiologic features of 1,383 infections. Medicine (Baltimore) 2000; 79: 109–23.
8. Landais C, Fenollar F, Thuny F, Raoult D: From acute Q fever to endocarditis: serological follow-up strategy. Clin Infect Dis 2007; 44: 1337–40.
9. Anderson AD, Smoak B, Shuping E, Ockenhouse C, Petruccelli B: Q fever and the US military. Emerg Infect Dis 2005; 11: 1320–2.
10. Leung-Shea C, Danaher PJ: Q fever in members of the United States armed forces returning from Iraq. Clin Infect Dis 2006; 43: e77–82.
11. Gleeson TD, Decker CF, Johnson MD, et al: Q fever in US military returning from Iraq. Am J Med 2007; 120: e11–2.
12. Hartzell JD, Peng SW, Wood-Morris RN, et al: Atypical Q fever in US soldiers. Emerg Infect Dis 2007; 13: 1247–9.
13. Faix DJ, Harrison DJ, Riddle MS, et al: Outbreak of Q fever among US military in western Iraq, June-July 2005. Clin Infect Dis 2008; 46: e65–8.
14. Ellis SB, Appenzeller G, Lee H, et al: Outbreak of sandfly fever in central Iraq, September 2007. Mil Med 2008; 173: 949–53.
15. Skiba V, Barner KC: Central nervous system manifestations of Q fever responsive to steroids. Mil Med 2009; 174: 857–9.
16. Ake JA, Massung RF, Whitman TJ, Gleeson TD: Difficulties in the diagnosis and management of a US servicemember presenting with possible chronic Q fever. J Infect 2010; 60: 175–7.
17. Anderson AD, Baker TR, Littrell AC, Mott RL, Niebuhr DW, Smoak BL: Seroepidemiologic survey for *Coxiella burnetii* among hospitalized US troops deployed to Iraq. Zoonoses Public Health 2011; 58: 276–83.
18. Hamilton LR, George DL, Scoville SL, Hospenthal DR, Griffith ME: PCR for rapid diagnosis of acute Q fever at a combat support hospital in Iraq. Mil Med 2011; 176: 103–5.
19. Voelker R: Risk of exposure to Q fever pathogen boosted by travel in Iraq or Netherlands. JAMA 2010; 303: 2345.
20. Fournier PE, Marrie TJ, Raoult D: Diagnosis of Q fever. J Clin Microbiol 1998; 36: 1823–34.
21. Hung MN, Chou YF, Chen MJ, et al: Q fever outbreak in a small village, Taiwan. Jpn J Infect Dis 2010; 63: 212–3.
22. Marrie TJ, Pollak PT: Seroepidemiology of Q fever in Nova Scotia: evidence for age dependent cohorts and geographical distribution. Eur J Epidemiol 1995; 11: 47–54.
23. Healy B, van Woerden H, Raoult D, et al: Chronic Q fever: different serological results in three countries—results of a follow-up study 6 years after a point source outbreak. Clin Infect Dis 2011; 52: 1013–9.
24. Turra M, Chang G, Whybrow D, Higgins G, Qiao M: Diagnosis of acute Q fever by PCR on sera during a recent outbreak in rural south Australia. Ann N Y Acad Sci 2006; 1078: 566–9.
25. Schneeberger PM, Hermans MH, van Hannen EJ, Schellekens JJ, Leenders AC, Wever PC: Real-time PCR with serum samples is indispensable for early diagnosis of acute Q fever. Clin Vaccine Immunol 2010; 17: 286–90.
26. Fenollar F, Fournier PE, Raoult D: Molecular detection of *Coxiella burnetii* in the sera of patients with Q fever endocarditis or vascular infection. J Clin Microbiol 2004; 42: 4919–24.
27. Million M, Thuny F, Richet H, Raoult D: Long-term outcome of Q fever endocarditis: a 26-year personal survey. Lancet Infect Dis 2010; 10: 527–35.
28. van der Hoek W, Versteeg B, Meekelenkamp JC, et al: Follow-up of 686 patients with acute Q fever and detection of chronic infection. Clin Infect Dis 2011; 52: 1431–6.
29. Fenollar F, Fournier PE, Carrieri MP, Habib G, Messana T, Raoult D: Risks factors and prevention of Q fever endocarditis. Clin Infect Dis 2001; 33: 312–6.
30. Limonard GJ, Nabuurs-Franssen MH, Weers-Pothoff G, et al: One-year follow-up of patients of the ongoing Dutch Q fever outbreak: clinical, serological and echocardiographic findings. Infection 2010; 38: 471–7.
31. Baddour LM, Wilson WR, Bayer AS, et al: Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation 2005; 111: e394–434.
32. Dupont HT, Thirion X, Raoult D: Q fever serology: cutoff determination for microimmunofluorescence. Clin Diagn Lab Immunol 1994; 1: 189–96.

33. Raoult D, Abbara S, Jassal DS, Kradin RL: Case records of the Massachusetts General Hospital. Case 5-2007. A 53-year-old man with a prosthetic aortic valve and recent onset of fatigue, dyspnea, weight loss, and sweats. N Engl J Med 2007; 356: 715–25.
34. Fournier PE, Casalta JP, Habib G, Messana T, Raoult D: Modification of the diagnostic criteria proposed by the Duke Endocarditis Service to permit improved diagnosis of Q fever endocarditis. Am J Med 1996; 100: 629–33.
35. Mylonakis E, Calderwood SB: Infective endocarditis in adults. N Engl J Med 2001; 345: 1318–30.
36. Frankel D, Richet H, Renvoisé A, Raoult D: Q fever in France, 1985-2009. Emerg Infect Dis 2011; 17: 350–6.
37. Fenollar F, Thuny F, Xeridat B, Lepidi H, Raoult D: Endocarditis after acute Q fever in patients with previously undiagnosed valvulopathies. Clin Infect Dis 2006; 42: 818–21.
38. Hartzell JD, Wood-Morris RN, Martinez LJ, Trotta RF: Q fever: epidemiology, diagnosis, and treatment. Mayo Clin Proc 2008; 83: 574–9.
39. Baggish AL, Hutter AM Jr, Wang F, et al: Cardiovascular screening in college athletes with and without electrocardiography: A cross-sectional study. Ann Intern Med 2010; 152: 269–75.
40. Reid CL, Anton-Culver H, Yunis C, Gardin JM: Prevalence and clinical correlates of isolated mitral, isolated aortic regurgitation, and both in adults aged 21 to 35 years (from the CARDIA study). Am J Cardiol 2007; 99: 830–4.
41. Lovey PY, Morabia A, Bleed D, Peter O, Dupuis G, Petite J: Long term vascular complications of *Coxiella burnetii* infection in Switzerland: cohort study. BMJ 1999; 319: 284–6.
42. Siegman-Igra Y, Kaufman O, Keysary A, Rzotkiewicz S, Shalit I: Q fever endocarditis in Israel and a worldwide review. Scand J Infect Dis 1997; 29: 41–9.
43. Sunder S, Gras G, Bastides F, De Gialluly C, Choutet P, Bernard L: Chronic Q fever: relevance of serology. Clin Infect Dis. 2011; 53: 749–50.
44. Lang RM, Bierig M, Devereux RB, et al: Recommendations for chamber quantification. Eur J Echocardiogr 2006; 7: 79–108.
45. Lang RM, Bierig M, Devereux RB, et al: Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005; 18: 1440–63.
46. Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA: Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr 2002; 15: 167–84.
47. Zoghbi WA, Enriquez-Sarano M, Foster E, et al: Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003; 16: 777–802.
48. Spyridaki I, Psaroulaki A, Vranakis I, Tselentis Y, Gikas A: In vitro susceptibility of *Coxiella burnetii* to linezolid in comparison with its susceptibilities to quinolones, doxycycline, and clarithromycin. Antimicrob Agents Chemother 2009; 56: 2690–2.
49. Lever MS, Bewley KR, Dowsett B, Lloyd G: In vitro susceptibility of *Coxiella burnetii* to azithromycin, doxycycline, ciprofloxacin and a range of newer fluoroquinolones. Int J Antimicrob Agents 2004; 24: 194–6.
50. Rolain JM, Maurin M, Raoult D: Bacteriostatic and bactericidal activities of moxifloxacin against *Coxiella burnetii*. Antimicrob Agents Chemother 2001; 45: 301–2.
51. Rolain JM, Lambert F, Raoult D: Activity of telithromycin against thirteen new isolates of *C. burnetii* including three resistant to doxycycline. Ann N Y Acad Sci 2005; 1063: 252–6.
52. Spyridaki I, Psaroulaki A, Vranakis I, Tselentis Y, Gikas A: Bacteriostatic and bactericidal activities of tigecycline against *Coxiella burnetii* and comparison with those of six other antibiotics. Antimicrob Agents Chemother 2009; 53: 2690–2.
53. Sobradillo V, Zalacain R, Capelastegui A, Uresandi F, Corral J: Antibiotic treatment in pneumonia due to Q fever. Thorax 1992; 47: 276–8.
54. Gikas A, Kofteridis P, Manios A, Pediaditis J, Tselentis Y: Newer macrolides as empiric treatment for acute Q fever infection. Antimicrob Agents Chemother 2001; 45: 3644–6.
55. Dijkstra F, Riphagen-Dalhuisen J, Wijers N, et al: Antibiotic therapy for acute Q fever in The Netherlands in 2007 and 2008 and its relation to hospitalization. Epidemiol Infect 2011; 139: 1332–41.
56. Domingo P, Muñoz C, Franquet T, Gurguí M, Sancho F, Vazquez G: Acute Q fever in adult patients: report on 63 sporadic cases in an urban area. Clin Infect Dis 1999; 4: 874–9.
57. Morovic M: Q fever pneumonia: are clarithromycin and moxifloxacin alternative treatments only? Am J Trop Med Hyg 2005; 73: 947–8.
58. Caron F, Meurice JC, Ingrand P, et al: Acute Q fever pneumonia: a review of 80 hospitalized patients. Chest 1998; 114: 808–13.
59. Carcopino X, Raoult D, Bretelle F, Boubli L, Stein A: Managing Q fever during pregnancy: the benefits of long-term cotrimoxazole therapy. Clin Infect Dis 2007 45: 548–55.
60. van der Hoek W, Meekelenkamp JC, Leenders AC, Wijers N, Notermans DW, Hukkelhoven CW: Antibodies against *Coxiella burnetii* and pregnancy outcome during the 2007-2008 Q fever outbreaks in The Netherlands. BMC Infect Dis 2011; 11: 44.
61. Munster JM, Leenders AC, van der Hoek W, et al: Cost-effectiveness of a screening strategy for Q fever among pregnant women in risk areas: a clustered randomized controlled trial. BMC Womens Health 2010; 10: 32.
62. Maurin M, Benoliel AM, Bongrand P, Raoult D: Phagolysosomal alkalinization and the bactericidal effect of antibiotics: the *Coxiella burnetii* paradigm. J Infect Dis 1992; 166: 1097–102.
63. Raoult D, Houpikian P, Tissot Dupont H, Riss JM, Arditi-Djiane J, Brouqui P: Treatment of Q fever endocarditis: comparison of 2 regimens containing doxycycline and ofloxacin or hydroxychloroquine. Arch Intern Med 1999; 159: 167–73.
64. Rolain JM, Boulos A, Mallet MN, Raoult D: Correlation between ratio of serum doxycycline concentration to MIC and rapid decline of antibody levels during treatment of Q fever endocarditis. Antimicrob Agents Chemother 2005; 49: 2673–6.
65. Lecaillet A, Mallet MN, Raoult D, Rolain JM: Therapeutic impact of the correlation of doxycycline serum concentrations and the decline of phase I antibodies in Q fever endocarditis. J Antimicrob Chemother 2009; 63: 771–4.
66. Marrie TJ: Q fever endocarditis. Lancet Infect Dis 2010; 10: 507–9.
67. Mogollón MV, Anguita MP, Aguado JM, et al: Q fever endocarditis in Spain. Clinical characteristics and outcome. Enferm Infecc Microbiol Clin 2011; 29: 109–16.
68. Landais C, Fenollar F, Constantin A, et al: Q fever osteoarticular infection: four new cases and a review of the literature. Eur J Clin Microbiol Infect Dis 2007; 26: 341–7.
69. Wegdam-Blans MC, Vainas T, van Sambeek MR, et al: Vascular complications of Q-fever infection. Eur J Vasc Endovasc Surg 2011; 42: 384–92.
70. Marmor MF, Kellner U, Lai TY, et al: Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. Ophthalmology 2011; 118: 415–22.